REMARKS

Claims 56-117 are currently pending in the application. Claims 78 and 86 are amended. Claims 69-77 and 87-117 are withdrawn. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Formal Matters

Priority

The Examiner notes that Applicants have not submitted certified copies of foreign application serial numbers UK0026099.2 (filed 10/25/00) and UK0015443.5 (filed 6/23/00). Applicants submit that they have requested certified copies of these two applications in order to perfect the priority claim, and will submit the certified copies to the Examiner as soon as they are received.

Claim Objections

The Examiner notes that claims 78 and 86 are objected to as being in improper dependent form as being dependent on a non-elected claim. Applicants submit that claims 78 and 86 have been amended to correctly depend from currently pending claims.

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Drawings

The Draftsperson has objected to the drawings on various grounds, including the need for Applicants to submit a full-tone set of photographs, and lack of uniform lines, numbers, and letters in Figures 1 and 8. Applicants submit that they have submitted herewith, substitute drawings. Accordingly, Applicants request that the Draftsperson's objections be withdrawn.

Rejection of Claims Under 35 U.S.C. §103

Buechler and Gordon

The Examiner has rejected claims 56-61 and 78-86 under 35 U.S.C. §103(a) as being obvious over the combined teachings of Buechler et al. (U.S. Pat. No. 6,057,098) in view of Gordon et al. (U.S. Pat. No. 5,489,452). The Examiner asserts that Buechler teaches a method of producing a multivalent polypeptide display library that can be used in diagnostic tests, wherein the polypeptides comprise V_H or V_L. The Examiner notes, however, that Buechler fails to teach that the polypeptide display library is applied to a solid surface. The Examiner asserts that Gordon discloses a method for immunological analysis consisting of a porous solid support containing an array of delimited adsorption areas of antigens and/or immunoglobulins. The Examiner asserts that Gordon teaches that the antigens or immunoglobulins can be applied in any suitable geometry such as dots, spots, or lines. The Examiner concludes that it would have been obvious to one of skill in the art to combine the teachings of polypeptides applied to the solid supports of Gordon with the methods taught by Buechler to arrive at the present invention. Applicants respectfully disagree with the Examiner.

For the reasons described below, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness under the requirements of 35 U.S.C. § 103(a). To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. Finally, the prior art reference (or references when combined) must teach or suggest ***all the claim limitations***. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

The claims of the present invention, in their broadest scope, relate to a method for screening a first repertoire of heavy or light chain polypeptides against a second repertoire of heavy or light chain polypeptides to identify members of the first and second repertoire which interact, wherein the first and second repertoires are arranged in at least two series of continuous lines such that the members of the first repertoire are juxtaposed to members of the second repertoire. The method of the invention may also include the step of contacting the array of first

and second repertoires with a target epitope to detect binding of the target epitope by the juxtaposed members of the first and second repertoire (claim 62). The method of the invention may also include contacting the array of first and second repertoires with a third repertoire comprising a target epitope arranged in a series of continuous lines and detecting the binding of the target by the juxtaposed first and second repertoire (claim 63). The claimed invention also encompasses a method whereby each of the first, second, and, if present, third repertoires are arranged as a series of lines and are provided as nucleic acid sequences which are expressed *in situ* on the array (claim 78). A requirement common to each embodiment of the claimed invention, therefore, is that the first and second repertoire of heavy or light chain polypeptides be each arranged in a *series of continuous lines*, such that *members of the first and second repertoire are juxtaposed*. Accordingly, to render obvious the claimed invention, any combination of references cited by the Examiner, when considered together or separately, must **at least teach two repertoires of heavy or light chain** polypeptide molecules **arranged in at least two series of continuous lines** such that a **plurality of members of the first repertoire are juxtaposed with a plurality of members of the second repertoire**. Applicants submit that the combination cited by the Examiner does not provide such a teaching, and thus the combinations cited by the Examiner do not teach each limitation of the claimed invention as required for a *prima facie* rejection under §103.

Buechler teaches methods for the production of multivalent polypeptide display libraries. Buechler teaches that a double chain antibody library may be generated by fusing one antibody chain to a phage coat protein, and then fusing a partner antibody chain to the first antibody chain, thus forming a Fab fragment which may be screened for antigen binding properties (col. 2, lines 35-45; col. 10, lines 8-14). As noted by the Examiner, *Buechler does not teach that either chain of a double chain antibody library may be applied to a solid surface*, and moreover, *does not teach that any member of a double chain antibody library is arranged in a series of continuous lines*.

Gordon teaches a device for immunological analysis in which antigens or immunoglobulin molecules are applied to a porous solid surface and then reacted with a test antibody or antigen (col. 2, lines 33-40), specifically, the support containing the antigens and/or immunoglobulins are immersed in a liquid sample to be analyzed (col. 8, lines 33-40). Gordon

teaches that the antigens or immunoglobulin molecules are applied to a solid support by direct contact, and may be applied as parallel lines which may then be cut into strips (col. 6, lines 25-33). Thus the teachings of Gordon provide that an antigen or immunoglobulin may be applied to a solid surface in a group of parallel lines which are then cut into strips and immersed in a liquid sample to detect the presence of a corresponding immunoglobulin or antigen. Gordon **does not** teach that a first and second repertoire of heavy or light chain polypeptide molecules is applied to a solid surface and are *arranged in at least two series of continuous lines such that members of the first repertoire are juxtaposed to members of the second repertoire.* Regardless of the nature of the molecules taught by either Gordon or Buechler, neither reference teaches or suggests the arrangement of a first and second repertoire of heavy or light chain polypeptides in at least two series of continuous lines, thus juxtaposing members of the first and second repertoire. Even if Buechler can be said to teach similar molecules to those claimed in the present invention (e.g., heavy or light chain polypeptide molecules), there is nothing in Gordon to suggest arranging the molecules in the claimed configuration to perform a method for screening a first and second repertoire to identify members of the first and second repertoire which interact. Applicants submit that Buechler and Gordong taken alone or together do not teach **at least teach two repertoires of heavy or light chain** polypeptide molecules **arranged in at least two series of continuous lines** such that a **plurality of members of the first repertoire are juxtaposed with a plurality of members of the second repertoire**. Therefore, Applicants submit that even if combined, the teachings of Buechler and Gordon do not teach each element of the claimed invention as required to make a rejection under §103.

Accordingly, Applicants submit that the invention is not obvious over Buechler and Gordon and request that the rejection be reconsidered and withdrawn.

Buechler and Miller

The Examiner has rejected claims 56-66 and 78-85 under 35 U.S.C. §103(a) as being obvious over Buechler et al. in view of Miller et al. (WO 99/39210). The Examiner asserts that Buechler teaches as described above, and that Miller teaches a method of determining the protein profile of a biological sample. The Examiner asserts that Miller teaches a primary array of proteins "wherein X_n is the coordinate along a first dimension of the array and Y_n is the

coordinate along a second dimension of the array. The Examiner asserts that Miller teaches screening the primary array with a plurality of antibodies and preparing a secondary array of antibodies that bind to the array. The Examiner concludes that one of skill in the art would have been motivated to include the polypeptides described by Buechler in the arrays of Miller to provide a screening system that could be readily applied to an entire proteome (citing Miller, p. 4, lines 21-23). Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness because, as described above, the combination of the references cited by the Examiner does not teach each aspect of the claimed invention.

Applicants have previously discussed the teachings of Buechler and will therefore not repeat them here, except to state that Buechler teaches double chain antibody libraries. Miller teaches a primary array of proteins, each with a specific coordinate on the array, indicated by the designation X_nY_n, wherein X is the coordinate along a first dimension of the array, and Y is the coordinate along a second dimension of the array. Miller teaches that each protein in the primary array is assigned an X_nY_n coordinate to facilitate its identification (p. 17, lines 25-26). Miller provides that an "array", according to the invention, is an ordered arrangement of proteins or antibodies, antibody variants or derivatives "on a grid, such as in microtitre wells or on a membrane support or silicon chip or on a grid comprising a plurality of polymeric pins" (p. 17, lines 10-13). Miller teaches that the primary array may be screened with a plurality of monoclonal antibodies and/or antibody variants and/or derivatives "one-at-a-time", or a reduced pool thereof "one-at-a-time" to determine those molecules which bind to one or more proteins in the primary array. A secondary array is then prepared, in a similar configuration to the primary array, on which is arrayed the monoclonal antibodies and/or antibody variants and/or derivatives which bound to proteins in the primary array. The secondary array is then screened with a biological sample to determine those proteins in the sample which bind to one or more of the monoclonal antibodies and/or antibody variants and/or derivatives in the secondary array (page 5-6).

There is no teaching in Miller that either of the primary or secondary array comprises a first and second repertoire of heavy or light chain polypeptides, and moreover, Miller does not teach that the proteins are arranged in *at least two series of continuous lines* such that members of the first repertoire are juxtaposed to members of the second repertoire. Applicants submit that

Buechler and Miller taken alone or together do not teach **at least teach two repertoires of heavy or light chain** polypeptide molecules **arranged in at least two series of continuous lines** such that a **plurality of members of the first repertoire are juxtaposed with a plurality of members of the second repertoire** as required by the claims of the instant invention. Even if Buechler can be said to teach similar molecules to those claimed in the present invention (e.g., heavy or light chain polypeptide molecules), there is nothing in Miller which teaches or suggests arranging the molecules in the claimed configuration (i.e., at least two series of continuous lines wherein a plurality of members of the first repertoire are juxtaposed to a plurality of members of the second repertoire) to perform a method for screening a first and second repertoire to identify members of the first and second repertoire which interact. Applicants therefore submit that even if combined, the teachings of Buechler and Miller do not teach each element of the claimed invention as required to make a rejection under §103.

Accordingly, Applicants submit that the instant invention is not obvious over Buechler and Miller, taken separately or together, and therefore request that the rejection be reconsidered and withdrawn.

Buechler and deWildt

The Examiner has rejected claims 56-68 and 78-86 under 35 U.S.C. §103 as being obvious over the teachings of Buechler et al., in view of deWildt et al. (Nature Biochemistry, 2000, 18:989). The Examiner asserts that deWildt teaches a method for screening antibody-antigen interactions, whereby many antibodies are screened in parallel against many antigens by a filter screening technique which involves the use of ordered arrays of antibodies generated by robot picking and gridding. The Examiner asserts that one of skill in the art would have been motivated to combine the teachings of Buechler and deWildt because the molecules of Buechler could be applied in the high throughput assays of deWildt comprising polypeptides applied to a solid support without "sticky" or cross reactive colonies (citing deWildt abstract). Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, because even if the teachings of both Buechler and deWildt were to be combined, one of skill in the art would not arrive at the claimed invention.

Buechler has been discussed above, and Applicants submit that Buechler teaches double chain antibody libraries. deWildt teaches the gridding of phage-antibody library colonies in a repeating 4x4 pattern on a first filter (p 993, second column, second paragraph). As shown in Figure 1A of deWildt, the array comprises discrete **spots** of the library colonies arranged in a repeating pattern. According to the method taught by deWildt, a second filter is coated with a binding partner for the arrayed antibody library (specifically, BSA or Protein-L; p 993, second column, second paragraph). The second filter is then placed in contact with the gridded colonies on the array, and an interaction between the arrayed antibodies and the binding partner coated on the second filter is detected. Applicants submit that deWildt clearly teaches that the antibody library molecules are present on the filter as spots and not lines. There is no teaching in deWildt that either the antibody library or the binding partner is arranged in a *series of continuous lines*. Further, there is no teaching in deWildt that either of the array or second filter comprises a first and second repertoire of heavy or light chain polypeptides arranged in *at least two series of continuous lines such that members of the first repertoire are juxtaposed to members of the second repertoire*. Applicants submit that Buechler and deWildt taken alone or together do not teach **at least teach two repertoires of heavy or light chain** polypeptide molecules **arranged in at least two series of continuous lines** such that a **plurality of members of the first repertoire are juxtaposed with a plurality of members of the second repertoire** as required by the claims of the instant invention. Even if Buechler can be said to teach similar molecules to those claimed in the present invention (e.g., heavy or light chain polypeptide molecules), there is nothing in deWildt which teaches or suggests arranging the molecules in the claimed configuration (i.e., at least two series of continuous lines wherein a plurality of members of the first repertoire are juxtaposed to a plurality of members of the second repertoire) to perform a method for screening a first and second repertoire to identify members of the first and second repertoire which interact. Applicants therefore submit that even if combined, the teachings of Buechler and deWildt do not teach each element of the claimed invention as required to make a rejection under §103.

Advantages of the present invention over the art cited

The Examiner has cited several combinations of prior art which the Examiner has asserted teach the present invention. Applicants submit that the present invention provides a

high throughput method for screening for interactions between repertoires of molecules. By arranging the first and second repertoires in series of lines, such that each member of the first repertoire is juxtaposed to each member of the second repertoire, the present invention provides a method wherein a large number of repertoire members may be screened, but wherein a minimal number of dispensing steps is required. More specifically, as taught in the specification on page 5, lines 1-12, the present invention provides a method for screening wherein the number of dispensing steps is always less than the number of interactions to be screened, and moreover, is significantly less than the number of dispensing steps required to perform the combinations asserted by the Examiner. Accordingly, the present invention allows one of skill in the art to screen a larger number of molecules than taught in the prior art with a lesser amount of dispensing steps, and thus a lesser amount of labor; making for a convenient high throughput screening assay.

Accordingly, Applicants submit that the present invention is not obvious over the teachings of deWildt and Buechler and therefore request that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

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